NAFLD and NASH: A Growing Problem in Adults and Adolescents

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Overview

• Epidemiology and Natural History of NAFLD.
• Current Challenges:
  • NAFLD is not a serious disease in young patients
  • There is no FDA-approved treatment for NAFLD
• Discuss the management of NAFLD today.
NAFLD is the Hepatic Manifestation of Obesity/IR

Metabolic Syndrome
- Insulin Resistance/ DM2
- Dyslipidemia
- Hypertension

- Elevated ALT
- Fatty liver on US

NAFLD
NAFLD Prevalence

• Adults
  • Overall: ~ 30%
  • Obese: ~ 50-70%
  • Severely Obese: 85%
  • DM2: ~ 65-75%

• Children
  • Overall: ~ 10%
  • 15-19 years: ~ 17%
  • Obese: ~ 50%

The NAFLD Spectrum

NAFL

NASH/Fibrosis

NASH Cirrhosis

HCC

80-100 Million

NAFLD Activity Score

<table>
<thead>
<tr>
<th>Steatosis (0-3)</th>
<th>5-33%</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>34-65%</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>≥66%</td>
<td>3</td>
<td></td>
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<table>
<thead>
<tr>
<th>Inflammation (0-3)</th>
<th>&lt;2 under 20x</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-4 under 20x</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>&gt;4 under 20x</td>
<td>3</td>
<td></td>
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<table>
<thead>
<tr>
<th>Ballooning (0-2)</th>
<th>Few</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Many</td>
<td>2</td>
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Challenge 1

NAFLD is not a serious disease in young patients
Burden of NAFLD Among Young Adults in the US

- National Health and Examination Survey (NHANES) database
- 14,371 subjects
- Age 18-35
- Three study periods:
  - 1988-1994
  - 1999-2004
  - 2005-2010

Young Kids, Old Bodies

Obesity is turning a generation of children into biological adults, ageing them before their time.
A hospital-based cohort study

n = 66 children with NAFLD, follow up for up to 20 years

- 2 patients developed NASH-cirrhosis that required LT at 20 and 25 years
LT for NASH in Children and Young Adults

Alkhouri et al. Transpl Int. 2016
NASH is the most rapidly increasing indication for OLT in young adults.
Challenge 2

There is no FDA-approved treatment for NAFLD
The Race to Cure NASH: Four Medications in Phase III RTCS

• **Obeticholic acid (OCA):** FXR agonist (REGENERATE)
• **Cenicriviroc:** CCR2/CCR5 inhibitor (STELLARIS)
• **Selonsertib:** Apoptosis signal-regulating kinase (ASK1) inhibitor (STELLAR-3 and -4)
• **Elafibranor:** PPAR α-δ agonist (RESOLVE IT)
Case Presentation

• A 55-year-old male with obesity (BMI of 40 kg/m2) presents to you with abnormal LFTs x 6 months.
• ALT 118 U/L, AST 106 U/L, with normal bilirubin, alkaline phosphatase and INR.
• On physical exam you notice mild hepatomegaly.
• Liver US showed diffuse increase in echogenicity and vascular blurring consistent with fatty infiltration. You suspect NAFLD.
How Do I Manage My Patient with NAFLD

1. Rule out other etiologies of elevated ALT or fatty infiltration of the liver.
3. Assess Severity (NASH, advanced fibrosis)
4. Treatment:
   • Lifestyle
   • Pharmacologic
Laboratory Assessment for NAFLD

Chronic Liver Disease Panel
- CBC + AUTO DIFF
- HEPATIC FUNCTION PNL
- GGT BLD
- BASIC METABOLIC PNL
- LIPID PANEL BASIC
- PROTHROMBIN TIME/PT
- HEP REMOTE PANEL BL
- HEP A AB TOTAL
- ANA BLOOD
- SMOOTH MUSCLE AB PNL SCRBN
- LKM AB
- ALPHA-1-ANTITRYPSIS BL
- IRON + TIBC
- FERRITIN BLD
- CERULOPLASMIN BLD
- CELIAC SCREEN WITH REFLEX
- CK CREATINE KINASE

NASH Panel
- CBC + AUTO DIFF
- HEPATIC FUNCTION PNL
- GGT BLD
- BASIC METABOLIC PNL
- LIPID PANEL BASIC
- TSH BLD
- HGB A1C
- INSULIN ASSAY BLOOD
- GLUCOSE FASTING BLD
- C-REACTIVE ULTRA SEN
- LIPOPROTEIN (A)
- ALBUMIN RANDOM URINE
- VITAMIN D 25 HYDROXY
Assessment of the Severity of NAFLD

NAFLD fibrosis score
Online calculator


Age (years) 
BMI (kg/m²) 
IGF/diabetes  
AST   
ALT   
Platelets (x10⁹/l)  
Albumin (g/l)  

calculate score
Algorithm for Assessing the Severity of NAFLD

Patient with NAFLD

NFS + VCTE

NFS < -1.455 and LSM < 7 kPa

- No advanced fibrosis
- Consider repeating every 2-3 years

Discordant results

Liver Biopsy

NFS > 0.676 and LSM > 10 kPa

- Advanced fibrosis
- Screen for cirrhosis complications
- US every 6 months
Treatment: % Weight Loss Associated With Histological Improvement

- Steatosis (35% - 100%)
  - Weight Loss ≥ 3%^{5,7,12-13}
- Ballooning/Inflammation (41% - 100%)
  - Weight Loss ≥ 5%^{5,7,12}
- NASH Resolution (64% - 90%)^{a}
  - Weight Loss ≥ 7%^{12}
- Fibrosis (45%)
  - Weight Loss ≥ 10%^{12}

The Mediterranean diet improves hepatic steatosis and insulin sensitivity in individuals with non-alcoholic fatty liver disease.

**HIGH IN:**
- MUFA
- PUFA
- Folate
- Fiber
- Antioxidants

**LOW IN:**
- Saturated Fat
- Ice cream
Testing:

- Fasting laboratory samples
- 3-hour euglycemic clamp study
- MRI/MRS
- Diet education and provision of food

Endpoints:

- Change in insulin sensitivity
- Change in hepatic steatosis

N = 12
Greater Reduction in Hepatic Fat and Greater Improvement in IS with MD than LFD

![Bar chart showing HTGC% for MD and LFD](chart1)

![Bar chart showing Change in GINF for MD and LFD](chart2)
Caffeine Intake is Protective Against NAFLD: Analysis of Population-Based Data from the US

Birerdinc A et al. *Aliment Pharmacol Ther.* 2012
Independent Predictors of NAFLD

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR (95% CI)</th>
<th>P</th>
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<tbody>
<tr>
<td>African American Race</td>
<td>0.520 (0.426-0.633)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.329 (1.132-1.562)</td>
<td>0.0007</td>
</tr>
<tr>
<td>Obesity (BMI ≥30)</td>
<td>2.087 (1.808-2.409)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Caffeine (mg) intake</td>
<td>0.999319 (0.998955-0.999684)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Total plain water consumed (g)</td>
<td>1.000065 (1.000008-1.000122)</td>
<td>0.0254</td>
</tr>
</tbody>
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Exercise: Aerobic or Resistance?
Both Resistance Training and Aerobic Training Reduce Hepatic Fat Content

Moderate/Vigorous Exercise: 30-45 min/day

Bacchi E et al. *Hepatology*. 2013
Changing the Attitude Toward Healthy Lifestyle in Texas
The NAFLD Lifestyle
Take Home Message

• NAFLD is very common and potentially serious liver disease even among children and young adults.

• NASH-specific therapies are coming soon and should change the attitude toward screening and treatment.

• Recommend coffee, Mediterranean diet, and exercise.